Absence of hexose-6-phosphate dehydrogenase results in reduced overall glucose consumption but does not prevent 11β-hydroxysteroid dehydrogenase-1-dependent glucocorticoid activation

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Hexose-6-phosphate dehydrogenase (H6PD) is thought to be the major source of NADPH within the endoplasmic reticulum (ER), determining 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) reaction direction to convert inert 11-oxo- to potent 11β-hydroxyglucocorticoids. Here, we tested the hypothesis whether H6pd knock-out (KO) in primary murine bone marrow-derived macrophages results in a switch from 11β-HSD1 oxoreduction to dehydrogenation, thereby inactivating glucocorticoids (GC) and affecting macrophage phenotypic activation as well as causing a more aggressive M1 macrophage phenotype. H6pdKO did not lead to major disturbances of macrophage activation state, although a slightly more pronounced M1 phenotype was observed with enhanced proinflammatory cytokine release, an effect explained by the decreased 11β-HSD1-dependent GC activation. Unexpectedly, ablation of H6pd did not switch 11β-HSD1 reaction direction. A moderately decreased 11β-HSD1 oxoreduction activity by 40-50% was observed in H6pdKO M1 macrophages but dehydrogenation activity was undetectable, providing strong evidence for the existence of an alternative source of NADPH in the ER. H6pdKO M1 activated macrophages showed decreased phagocytic activity, most likely a result of the reduced 11β-HSD1-dependent GC activation. Other general macrophage functions reported to be influenced by GC, such as nitrite production and cholesterol efflux, were altered negligibly or not at all. Importantly, assessment of energy metabolism using an extracellular flux analyzer and lactate measurements revealed reduced overall glucose consumption in H6pdKO M1 activated macrophages, an effect that was GC independent. The GC-independent influence of H6PD on energy metabolism and the characterization of the alternative source of NADPH in the ER warrant further investigations. ENZYMES: 11β-HSD1, EC 1.1.1.146; H6PD, EC 1.1.1.47.

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